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Isoquinoline alkaloids of *Zanthoxylum quinduense* (Rutaceae)

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1. Subject and source

The genus *Zanthoxylum* (*Rutaceae*) comprises some 549 species worldwide distributed mainly in tropical and temperate regions. *Z. quinduense* Tul. [syn. *Fagara quinduense* (Tul.) Engl., *F. macrosperma* (Tul.) Engl., *Z. macrospermum* (Tul.)] is a tree that grows in South America and it is mainly found in Colombia, Venezuela, Ecuador and Peru (Global Biodiversity Information Facility, 2010).

Plant material from *Z. quinduense* (Tul) was collected during August 2005 in the town of Alban, Cundinamarca department, Colombia and identified by biologist Zaleth Cordero. A voucher specimen (COL 511101) has been deposited at Herbario Nacional Colombiano, Instituto de Ciencias Naturales, Universidad Nacional de Colombia.

2. Previous work

Chemical studies carried out on *Zanthoxylum* species have revealed the occurrence mainly of alkaloids, lignans, amides and coumarins. The alkaloids commonly found in species of the genus *Zanthoxylum* belong to groups of isoquinoline (mainly benzo[*c*]phenanthridine-type) and quinoline (Mester, 1983; Krane et al., 1984; Adesina, 2005). Previous phytochemical investigations on *Z. quinduense* led to the isolation of six benzophenanthridine alkaloids (8-hydroxy-2,3-methylenodioxy-9-methoxybenzophenanthridine, norchelerythrine, 6-acetonyldihydrochelerythrine nornitidine, arnottianamide and decarine), one lignan (syringaresinol), one phenylpropene (evofolin-*C*), two benzenoids (*p*-hydroxybenzaldehyde and vanillic acid), three sterols (β-sitosterol, stigmasterol and campesterol), one triterpene (lupeol) and a mixture of saturated and unsaturated fatty acids, and their derived methyl esters from extracts of the wood and/or bark (Patiño and Cuca, 2004, 2007, 2010).

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3. Present study

Air-dried and powdered bark of *Z. quinduense* (396.5 g) was exhaustively extracted with 96% ethanol by maceration at room temperature. The solvent was evaporated under vacuum to afford 61.3 g of the crude extract. A part of this residue (55 g) was extracted with H_2O–Et_2O 1:1 mixture (600 mL) assisted by ultrasound and acidified with 2 N HCl to pH 2.0. The organic phase was separated and the aqueous layer was extracted with Et_2O (3 × 60 mL). The Et_2O phases gave negative test with Dragendorff's reagent, so was not analyzed. The aqueous acidic solution was basified with NH_4OH to pH 9.0 and successively partitioned with $CHCl_3$ (3.0 g) and $CHCl_3$–EtOH 8:2 mixture (1.3 g).

The $CHCl_3$ fraction (2.5 g) was subjected to flash chromatography (FC) over silica gel (230–400 mesh) and eluted with increasing polarity mixture of $CHCl_3$–MeOH (10:0 to 7:3) affording 16 fractions. The fraction 2 (253.4 mg) was purified by FC eluting with *n*-hexane-AcOEt 8:2 to obtain lupeol (**1**, 12.5 mg) (Olea and Roque, 1990) and nornitidine (**2**, 6.4 mg) (Sukari et al., 1999). The fractions 4–6 were recombined (285.6 mg) and submitted to successive silica gel FC eluting with *n*-hexane-AcOEt 8:2, and CH_2Cl_2–MeOH 98:2 to give norchelerythrine (**3**, 7.3 mg) (Tousek et al., 2004) and (-)-6-acetonyldihydrochelerythrine (**4**, 4.5 mg) (Martínez-Martínez et al., 2002). Fraction 8 (226.4 mg) was subjected to successive FC eluting with *n*-hexane-AcOEt 7:3, $CHCl_3$ and CH_2Cl_2–AcOEt 9:1 to obtain decarine (**5**, 5.3 mg) (Martin et al., 2005). (-)-6-Carboxymethyldihydrochelerythrine (**6**, 9.3 mg) (Ng et al., 1987) was isolated of the fraction 10 (151.2 mg) by successive FC eluted with *n*-hexane-acetone 7:3, *n*-hexane-AcOEt 5:5 and $CHCl_3$–AcOEt 8:2.

The $CHCl_3$–EtOH fraction (1.0 g) was submitted to FC over silica gel (230–400 mesh) and eluted with increasing polarity mixture of $CHCl_3$–MeOH (90:10 to 70:30) yielding 13 fractions. The fraction 1 (15.2 mg) was isolated chelerythrine (**7**, 4.6 mg) (Krane et al., 1984) by FC eluting with CH_2Cl_2–MeOH 95:5. Fraction 3 (31.6 mg) was purified by FC eluting with CH_2Cl_2–MeOH 9:1 to give berberine (**8**, 8.5 mg) (Tripathi et al., 2007). The collected fractions 5–7 (256.5 mg) were purified by successive FC eluting with $CHCl_3$–MeOH 85:15, $CHCl_3$:MeOH 8:2 and CH_2Cl_2:MeOH 85:15 to obtain a mixture of *N*-methyltetrahydrocolumbamine and *N*-methyltetrahydropalmatine (**9** and **10**, respectively, 8.8 mg) (Guo et al., 1999; Likhitwitayawuid et al., 1993). Fraction 8 (177.3 mg) was isolated (-)-isotembetarine (**11**, 70.4 mg) (Moriyasu et al., 1997) by FC eluting with $CHCl_3$–MeOH 8:2. Fractions 9–10 were recombined (225 mg) and subjected to successive FC eluting with $CHCl_3$–MeOH 8:2, CH_2Cl_2–MeOH 8:2 and $CHCl_3$–MeOH 7:3 to obtain (-)-xylopinidine (**12**, 22.8 mg) (Nishiyama et al., 2004). The isolated compounds (Fig. 1) were identified based on spectroscopic analysis (HRMS, EIMS, IR, ^{1}H and ^{13}C NMR, 2D NMR) and by comparison of their spectral data with those reported in the literature. Absolute configuration of some isolated chiral alkaloids was established by means of optical rotation and/or circular dichroism measurements.

Compound **11** was obtained as yellowish oil and analyzed for the molecular formula $C_{20}H_{25}NO_4^+$ by HRMS $[M\text{-}1]^{+\cdot}$ at *m/z* 343.1785 (calcd. 343.1784), which was supported by its NMR data. The ^{1}H and ^{13}C NMR spectra of **11** together with DEPT, COSY, HMQC and HMBC analysis indicated the presence of general structure in common with a benzylisoquinoline alkaloid named isotembetarine, which was previously isolated from the stems of *Zanthoxylum nitidum* (Moriyasu et al., 1997). The optical rotation of **11** was similar but of opposite sign ($[\alpha]_D^{20}$ −5.5) to that of (*R*)-(+)-isotembetarine ($[\alpha]_D^{25}$ + 3.5°), hence, **11** is the enantiomer (+)-isotembetarine. The absolute configuration was confirmed from CD measurements (positive Cotton effect at 210, 234 250 and 280 nm) on comparing with data reported for (*R*)-(+)-isotembetarine, indicating to C-6 as *S*. Therefore, **11** was identified as *(S)-(-)*-isotembetarine. Similarly **12** was identified as *(-)*-xylopinidine and its configuration determined as *R* by CD measurements (negative Cotton at 210, 234, 250 and 281 nm) and comparing the data with several benzylisoquinoline alkaloids (Moriyasu et al., 1997). Some spectral data and physical constants have not been reported yet these data are presented.

(-)-6-acetonyldihydrochelerythrine **4**: white solid, mp 188–192 °C ($CHCl_3$), $[\alpha]_D^{20}$ −135 (*c* 0.13, $CHCl_3$).
(-)-6-carboxymethyldihydrochelerythrine **6**: yellow solid, mp 222–225 °C ($CHCl_3$), $[\alpha]_D^{20}$ −65.6 (*c* 0.13, $CHCl_3$).

(S)-(-)-isotembetarine **11**: yellowish oil, $[\alpha]_D^{20}$: −5.5 (*c* 0.45, MeOH), CD (TFE/H_2O 3:7): $[\theta]_{280}$ + 12 400, $[\theta]_{250}$ + 149, $[\theta]_{234}$ + 3049, $[\theta]_{208}$ + 6777; ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD): δ 6.73 (d, *J* = 8.4 Hz, 1H, H-6), 6.65 (s, 1H, H-2′), 6.62–6.51 (m, 2H, H-5, H-5′), 6.43 (d, *J* = 8.2 Hz, 1H, H-6′), 4.77 (d, *J* = 4.0 Hz, 1H, H-1), 3.70 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.51 (td, *J* = 12.4, 6.4 Hz, 1H, H-3a), 3.29 (dd, *J* = 11.9, 5.4 Hz, 1H, H-3b), 3.12–3.04 (m, 2H, H-α), 3.00 (dd, *J* = 13.7, 6.2 Hz, 1H, H-4a), 2.94 (s, 3H, NCH_3), 2.87 (s, 3H, NCH_3), 2.85–2.68 (m, 1H, H-4b); ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD): δ 146.4 (C-4′), 145.8 (C-7), 145.7 (C-3′), 142.3 (C-8), 129.5 (C-1′), 120.1 (C-6′), 120.0 (C-4a), 119.0 (C-5), 118.2 (C-8a), 115.4 (C-2′), 111.6 (C-6), 111.4 (C-5′), 69.1 (C-1), 55.7 (OCH_3), 55.4 (OCH_3), 54.0 (C-3), 53.0 (NCH_3), 50.7 (NCH_3), 36.5 (C-α), 22.4 (C-4); HRMS $[M\text{-}1]^{+\cdot}$ *m/z* 343.1785 (calcd. for $C_{20}H_{25}NO_4^+$ 343.1784); EIMS *m/z* (%) 344 (23), 343 (100), 273 (58), 253 (24), 230 (19), 193 (21), 181 (23), 151 (25), 137 (36).

(R)-(-)-xylopinidine **12**: yellowish oil, $[\alpha]_D^{20}$: −72.5 (*c* 0.13, MeOH), CD (TFE/H_2O 3:7): $[\theta]_{281}$ − 3486, $[\theta]_{250}$ − 395, $[\theta]_{234}$ − 6095, $[\theta]_{210}$ −8228; ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD): δ 6.60 (s, 1H, H-2), 6.56 (d, *J* = 7.8 Hz, 1H, H-5′), 6.51 (s, 1H, H-8) 0.6.16 (d, *J* = 7.6 Hz, 1H, H-6′), 5.94 (s, 1H, H-5), 4.56 (s, 1H, H-1), 3.71 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.57–3.43 (m, 2H, H-3), 3.39–3.29 (m, 1H, H-α), 3.27 (s, 3H, NCH_3), 3.04 (s, 3H, NCH_3), 2.92 (d, *J* = 16.7 Hz, 2H, H-4), 2.77 (sa, 1H, H-α); ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD): δ 148.0 (C-7), 146.7 (C-4′), 146.0 (C-3′), 144.8 (C-6), 127.1 (C-1′), 122.1 (C-4a),121.0 (C-6′), 118.4 (C-8a), 115.8 (C-2′), 114.4 (C-5), 111.3 (C-5′), 110.6 (C-8), 72.2 (C-1), 55.5 (OCH_3), 55.4 (OCH_3), 54.8 (C-3), 52.1 (NCH_3), 50.8 (NCH_3), 37.7 (C-α), 23.2 (C-4); HRMS $[M\text{-}1]^{+\cdot}$ *m/z* 343.1784 (calcd. for $C_{20}H_{25}NO_4^+$ 343.1787); EIMS *m/z* (%) 343 (13), 206 (11), 193 (13), 192 (100), 177 (57), 148 (12), 137 (17).

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